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The administration of psilocybin to healthy, hallucinogen-experienced volunteers in a mock-functional magnetic resonance imaging environment: a preliminary investigation of tolerability

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Abstract

This study sought to assess the tolerability of intravenously administered psilocybin in healthy, hallucinogen-experienced volunteers in a mock-magnetic resonance imaging environment as a preliminary stage to a controlled investigation using functional magnetic resonance imaging to explore the effects of psilocybin on cerebral blood flow and activity. The present pilot study demonstrated that up to 2 mg of psilocybin delivered as a slow intravenous injection produces short-lived but typical drug effects that are psychologically and physiologically well tolerated. With appropriate care, this study supports the viability of functional magnetic resonance imaging work with psilocybin.

Keywords

hallucinogen, psilocybin, psychedelic

Introduction

Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) is a tryptamine hallucinogen and the pro-drug of psilocin (4-hydroxy-N,N-dimethyltryptamine), a partial agonist at the 5-HT2A receptor (Nichols, 2004) and the active constituent of psilocybe mushrooms. In the late 1950s, psilocybin was identified and isolated from its natural source (Hofmann et al., 1958, 1959). Like the pharmacologically related hallucinogen, lysergic acid diethylamide (LSD), psilocybin was commonly used as an adjunct to psychoanalytic psychotherapy for the treatment of a wide range of psychiatric conditions (Grinspoon and Bakalar, 1979; Leuner, 1963). In the mid-1960s, the popularization of hallucinogenic drugs stimulated an increase in recreational use. Subsequent adverse events attracted media attention and public and political concern, leading to the withdrawal of production (Spencer, 1966) and the introduction of significant restrictions on research (Lee and Shlain, 1985). It has only been in the last 15 years or so that clinical researchers have begun to work again with this group of compounds (Griffiths et al., 2006; Vollenweider et al., 1997).

Functional MRI (fMRI) has emerged as a powerful imaging modality, but psilocybin has never been administered in this environment. Recent guidelines for human research with hallucinogens cautioned against exposing 'intoxicated' subjects to potentially anxiogenic situations (Johnson et al., 2008). In accordance with this advice, the present study sought to assess the tolerability of intravenously administered psilocybin in healthy, hallucinogen-experienced volunteers in a mock-fMRI setting as a preliminary stage to a controlled investigation using this imaging modality. Intravenous administration was chosen on the basis of previous work indicating good tolerability and a fast onset and brief duration of subjective effects (Hasler et al., 1997), convenient for fMRI studies.

Methods

Subjects

This study was approved by an NHS Research Ethics Committee and conducted in accordance with the

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Declaration of Helsinki and Good Clinical Practice guidelines.

Subjects were recruited via word of mouth. All subjects gave written informed consent. Nine subjects participated in the study, seven males and two females. Mean age was 35.8 (SD 4.9, range 28–43). Subjects were physically and mentally healthy with no personal or family history of psychiatric illness. All subjects were required to have taken a hallucinogenic drug on at least one occasion without adverse reaction.

Screening

Subjects were screened in a clinical research unit in the Bristol Royal Infirmary. Demographic information was recorded and medical history taken. A physical examination, including electrocardiogram (ECG), routine blood tests, and urine test for drugs of abuse and pregnancy were carried out. A psychiatric assessment was conducted and participants gave full disclosure of their drug taking histories. Participants completed the State Trait Anxiety Inventory (STAI) and the Beck Depression Inventory (BDI). Exclusion criteria were: less than 27 years of age, pregnancy, current or previously diagnosed psychiatric disorder, immediate family member with a current or previously diagnosed psychiatric disorder, substance dependence (including alcohol), cardiovascular disease, claustrophobia, blood or needle phobia, or a significant acute or persistent adverse response to a hallucinogenic drug.

Drug session

Three subjects received 1.5 mg psilocybin before ethics permission was sought to increase the dose to 2 mg, and six participants received 2 mg psilocybin after establishing the tolerability of the lower dose. All drug sessions took place in a clinical research unit in the Bristol Royal Infirmary. Prior to the subjects' arrival, a wooden mock-MR scanner was placed on an examination bed in a consulting room, the mock-scanner consisted of a flat wooden board, approximately 7 ft in length and 3 ft wide, and a wooden arch/tube which was placed over the board. The arch was approximately 4 ft long and 3 ft wide and covered subjects' upper body, replicating well the dimensions of a real MR scanner. All subjects were made aware at screening that the mock-scanner was a replica and they were also aware of the dose they would receive and its expected effects.

On arrival, a urine test for drugs of abuse and pregnancy was carried out and subjective ratings were given. Subjects were cannulated and allowed to enter and habituate to the mock-scanner. Subjects placed their head inside a wooden mock-head coil and a small mirror fixed to the roof of the mock-scanner allowed them to see out. Beyond these measures, movement was not restricted. An auditory recording of fMRI scanner noise was played in the last three dosing sessions, once we were confident of tolerability, and subjects were habituated to this.

A light-protected vial of psilocybin, commercially procured and certified for purity, was stored in a locked refrigerator at approximately 5°C. For each session, shortly before administration, approximately 3.5 mg psilocybin was weighed and reconstituted with saline to give a 1 mg:1 ml solution. The solution was then passed through a minisart 0.2 gm sterile filter into a sterile, nitrogen-filled vial.

Prior to administration, subjects rated how: 'happy', 'sleepy', 'relaxed', 'anxious', and 'confused' they felt on a 0–10 scale (0 being 'none' or 'not at all' and 10 being 'extreme' or 'extremely'). Either 1.5 ml or 2 ml of the psilocybin solution was drawn up by the study psychiatrist and made up to a total of 10 ml with saline to give doses of 1.5 and 2 mg respectively. The 10 ml solution was administered over 60 s, the end of the infusion being taken as time zero. The subject rated the intensity of the drug effects on a 0–10 scale (0 being 'no drug effects' and 10 being 'extremely intense drug effects') at 1 min intervals for 20 min and cardiovascular data (heart rate and blood pressure) were acquired for 3 min before and 20 min after the bolus.

Subjects remained in the mock-scanner for approximately 25 min after the drug was given; they were then assisted out of the mock-scanner and seated in a comfortable space while the drug effects subsided. After exiting the mock-scanner, subjects gave retrospective ratings for: drug effects, happy, sleepy, relaxed, anxious, and confused on a 0–10 scale, according to how they felt when the drug effects were most intense. Over the next 60–90 min subjects completed the 5-Dimensions of Altered States of Consciousness questionnaire (5D-ASC) (Dittrich 1998, translated from the original German into English by Felix Hasler and Rael Cahn), a 94-item self-rated questionnaire. The 5D-ASC is completed as a Likert scale. It measures five key dimensions: 'oceanic boundlessness' (which identifies mystical-type experiences and has been compared with the 'heaven' aspect of Huxley's mescaline account [Dittrich, 1998]), 'anxious ego dissolution' (analogous to a 'bad trip' or Huxley's 'hell' dimension [Dittrich, 1998]), 'visionary restructuralization' (essentially a measure of visual distortions/hallucinations which, for accessibility, we refer to as 'visual alterations'), 'auditory alterations', and 'reduced vigilance' (see Dittrich et al., 1998 and Hasler et al., 2004 for more detailed descriptions of this rating scale). The 5D-ASC global score is the product of the scores on the dimensions 'oceanic boundlessness', 'anxious ego dissolution', and 'visual alterations'. Subjects were allowed to leave the clinic once the subjective effects had fully subsided. Subjects received a follow-up phone call in the evening and were also given emergency contact details in case of any unexpected adverse phenomena. All subjects were contacted 14 days after having received the drug for an informal check-up.

Results

Demographics and personality factors

Nine subjects participated in this study, seven males and two females. Mean age was 35.8 years old (SD 4.9, range 28–43). All subjects had used psilocybin mushrooms before (mean 17.9 previous uses, SD 19.1, range 1–50). Last use of psilocybin ranged from 10 months to 5 years (mean 18.4, SD 15.9). All subjects gave relatively low, clinically non-significant ratings on the BDI (mean 1.3, SD 1.2, range 0–3) and

STAI (mean 28.4, SD 5.5, range 22–41). Table 1 summarizes the demographics and personality ratings recorded at screening.

Acute effects

Three subjects received 1.5 mg psilocybin. This dose produced mild to moderate subjective effects. Subjects described a fast onset; all three described entering a pleasant 'meditatory' state, sensations of warmth and mild proprioceptive and visual distortions (e.g. a feeling of floating in space and an appearance of 'breathing' movements in surfaces). Simple ratings of 'drug-effects' peaked at 5/10, 3/10, and 8/10 in the first three subjects. Effects were first noticed approximately 60 s after the end of the infusion, peaking after approximately 5 min and subsiding thereafter (Figure 1). Heart rate (HR) and blood pressure (BP) increases were transient and did not exceed 20 bpm or 20 mmHg. No acute or subacute adverse phenomena were reported. After the effects had subsided, all subjects reported having found the experience pleasant and interesting but relatively mild.

Six subjects received 2 mg psilocybin. All six subjects reported significant effects, beginning at the end of the 60 s bolus, peaking after approximately 4 min, and sustaining for approximately 20 min (Figure 1). Ratings of peak 'drug effects' ranged from 5 to 8.5/10. Subjects described sensations of warmth and some described becoming conscious of an increase in their heart rate. Subjects showed transient heart rate increases of ~15 bpm and systolic blood pressure (SBP) increases of ~20 mmHg. The same basic proprioceptive and perceptual distortions (e.g. sensations of floating and an appearance of breathing movements in surfaces) were described as for the lower dose. During the initial onset, some subjects described 'quite strong' drug effects. Synaesthesia was described by one subject (sounds influencing visual percepts) and this was also evident in other subjects' 5-D ASC ratings. Several subjects reported an altered sense of time (also seen in 5-D ASC ratings). There were no indications of distress during the acute experience and all subjects reported having found it interesting and insightful. The noise from the fMRI scanner was played in the last three sessions once we felt confident about dose tolerability and there were no adverse reactions. Subjects' ratings at each time point were compared using a repeated measures ANOVA (Figure 1).

Table 1. Demographics and personality ratings recorded at screening (mean values and standard deviation). There were no significant differences between demographic or personality variables for the two dosing groups (independent samples *t*-tests, two-tailed, $\alpha = 0.05$).

	All subjects	1.5 mg	2 mg
N	9	3	6
Age	35.8 (4.9)	37.3 (2.3)	35 (5.8)
Previous uses of psilocybin	17.9 (19.1)	5 (6.1)	24.3 (20.4)
Months since last use of psilocybin	18.4 (15.9)	27.3 (28.3)	14 (3.3)
Sex	7 males, 2 females	3 males, 0 females	4 males, 2 females
BDI	1.3 (1.2)	1.3 (1.2)	1.3 (1.4)
STAI	28.4 (5.5)	30.3 (9.7)	27.5 (2.9)

BDI: Beck Depression Inventory, STAI: State Trait Anxiety Inventory.

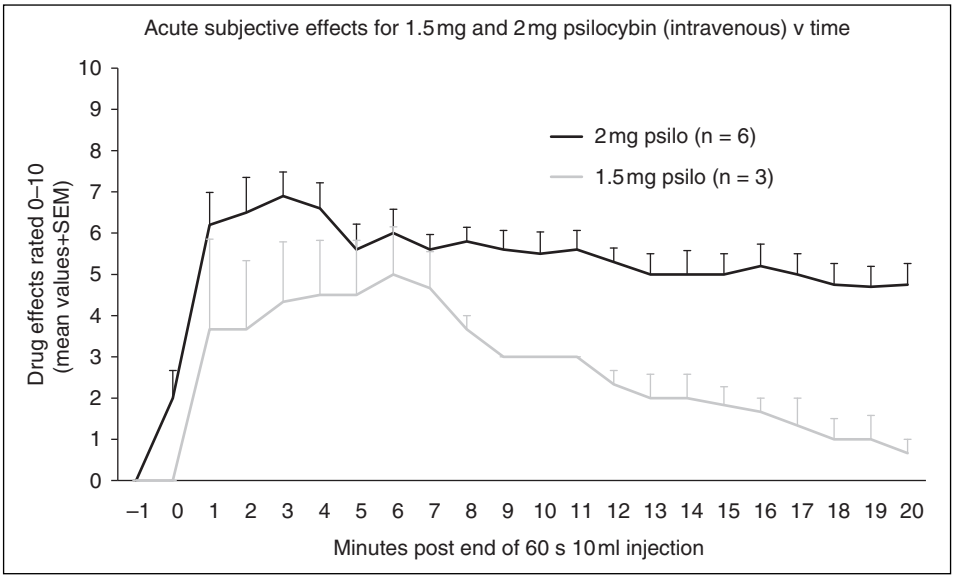

Figure 1. Subjects' ratings at each time point were compared using a repeated measures ANOVA, with time as the within subjects variable and dose as the between subjects variable. A significant effect of time ($F = 15.2$, d.f. $= 21$, $p = <0.001$), dose × time ($F = 2$, d.f. $= 21$, $p = 0.01$), and dose was found ($F = 10.3$, d.f. $= 1$, $p = 0.005$). The 0–10 ratings were anchored with 0 being 'no noticeable drug effects' and 10 being 'extremely intense effects'. Time zero corresponds to the end of the 60 s injection.

Post-drug ratings

Subjects were asked to provide retrospective ratings for the period of peak drug effects. Rated 0–10, the mean rating (SD, range) for 'happy' after 1.5 mg psilocybin was 8/10 (±2, 6–8) and after 2 mg it was 8.3/10 (±0.8, 7–9); for 'relaxed', the mean rating after 1.5 mg was 8.7/10 (±1.2, 8–10) and after 2 mg it was 7.3/10 (±2.7, 4–10). These ratings indicated that the experience had been well-tolerated. Corroborating this, the mean rating for 'anxiety' after 1.5 mg was 2.7/10 (±3.8, 0–7) and after 2 mg it was 3.8/10 (±3.2, 0–8); for 'confusion' after 1.5 mg all subjects gave a rating of 0, and after 2 mg the mean rating was 1.7/10 (±2.1, 0–5). When compared against the pre-drug baseline, none of these ratings had significantly increased or decreased (related t-tests, $\alpha = 0.05$, two-tailed; see Figure 2). Although the apparent increase in anxiety (Figure 2) was non-significant (related t-test, $t = 1.53$, $p = 0.17$, two-tailed), two subjects did give quite high ratings for 'anxiety' at peak effects, i.e. one subject at 1.5 mg rated it 7/10 (up from 1/10 pre-drug) and another at 2 mg rated it 8/10 (up from 1/10 pre-drug). The high ratings were transient in both cases, neither subject reported discomfort or distress, and both reported having found the experience pleasant, with one reporting 'deeply felt positive mood'. These findings support the notion that simple mood ratings do not capture the essence of the 'psychedelic' ('soul-manifesting', Osmond, 1957) experience. The mean ratings given retrospectively for the peak drug effects minus the mean pre-drug ratings are shown in Figure 2.

5-Dimensions of Altered States of Consciousness rating scale

After the acute drug effects had subsided, subjects completed the 5-D ASC. Global and subscale ratings were generally lower for subjects administered 1.5 mg, but not to a statistically significant degree. At 1.5 mg, the mean global rating was roughly consistent with ratings previously recorded after a 'low' oral dose of psilocybin (i.e. ~8 mg), and at 2 mg, mean global ratings were roughly consistent with ratings recorded after a 'medium' oral dose of psilocybin (i.e. ~15 mg) (Hasler et al., 2004). Figure 3 shows the ratings for the 94-item 5-D ASC expressed as a percentage of the maximum possible ratings for each dimension.

Follow-up

Subjects were followed up 14 days after the drug experience and asked to complete a second copy of the BDI and STAI. No statistically significant changes in psychiatric ratings were observed relative to screening and no persistent adverse events were reported. Subjects were asked how they would anticipate the drug experience being tolerated in a real MR scanner; all subjects expressed an opinion that the experience would be well tolerated.

Discussion

Summary of findings

In a mock-MRI setting, intravenously administered psilocybin was psychologically and physiologically well tolerated by nine healthy, hallucinogen-experienced volunteers. A dose of 2 mg psilocybin produced significantly stronger subjective effects than 1.5 mg according to 0–10 'drug effects' ratings, with a faster onset and longer duration of effects. No acute or subacute adverse phenomena were reported. All subjects expressed an opinion that the drug experience would be tolerable in a real MR scanner.

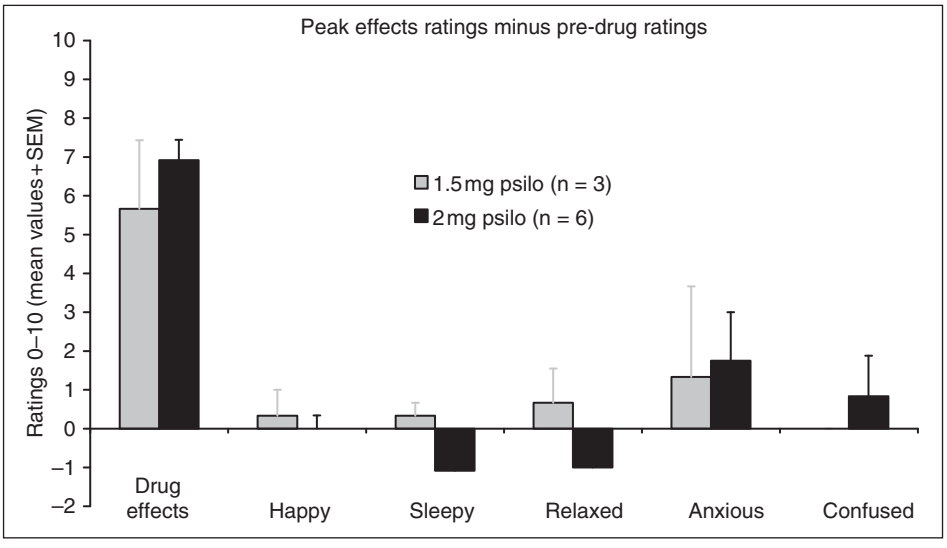

Figure 2. Mean ratings given retrospectively for the peak drug effects minus the mean pre-drug ratings. Apart from 'drug effects', peak effects ratings were not significantly different to the pre-drug ratings for any of the variables (related t-tests, $\alpha = 0.05$, 2- tailed). Ratings for the two doses also did not significantly differ (independent samples t-test, $\alpha = 0.05$, two-tailed).

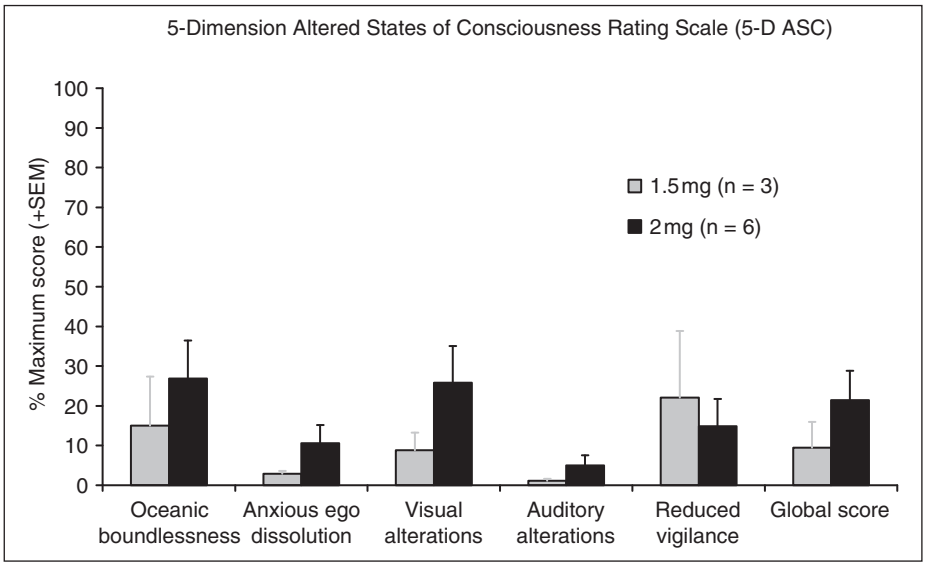

Figure 3. Ratings for the 94-item 5-D ASC expressed as a percentage of the maximum possible ratings for each dimension. The scale was completed within 90 min of the drug experience. Ratings for the two doses were not significantly different from each other on any of the dimensions (independent samples t-test, $\alpha = 0.05$, two-tailed).

Implications

This pilot investigation was designed to assess the tolerability of psilocybin, a potential anxiogen, in a potentially anxiogenic (MR scanner) environment. Although psilocybin has been administered in positron emission tomography (PET) settings before (Gouzoulis-Mayfrank et al., 1999; Vollenweider et al., 1997), it has never been given in the relatively more restrictive and noisy MR environment. It was reassuring to discover that all subjects responded well to the drug in this environment. In fact, the enclosed environment seemed reasonably well suited to the experience, enabling subjects to lie still, without distraction. We observed no problems with movement and the subjects who listened to scanner noise were unperturbed by it.

Previous work has indicated that subjects are uniquely sensitive to the environment in which the psychedelic experience takes place (Johnson et al., 2008). We treated our subjects in a friendly, supportive manner and sought to improve the aesthetics of the experimental setting. It is likely that this contributed to the subjects' positive responses. It might be informative to control for 'environment' in future human hallucinogen research by including it as an independent variable, while maintaining good ethical standards (Johnson et al., 2008).

It is apparent that intravenous psilocybin is subject to a steep dose-response curve, i.e. a relatively small increase in dose produces a substantial increase in drug effects. In the only previous report on intravenous psilocybin in humans, adverse effects (e.g. fear, derealization, vomiting, and cardiovascular effects) were reported after 3 mg psilocybin in one pilot subject that lasted for approximately 10 min (Hasler et al., 1997). Increasing the intravenous dose of psilocybin above 2 mg would increase the risk of adverse events. If doses greater than 2 mg are considered, slower infusion periods are advised.

Conclusions

Intravenous psilocybin administered in doses up to 2 mg is psychologically and physiologically well-tolerated in healthy, hallucinogen-experienced volunteers in a mock-fMRI setting. No significant acute or persistent adverse phenomena were reported. This work supports the view that, if careful consideration is given to screening and subject care, psilocybin can be safely administered to healthy human volunteers in a controlled fMRI setting.

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